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Research report

# Chronic forced exercise during adolescence decreases cocaine conditioned place preference in Lewis rats

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ABSTRACT

Chronic physical activity (exercise) may be beneficial in the prevention of substance use disorders; however, the extent to which physical activity can interfere with the reinforcing effects of drugs during the adolescent period, which is one of great vulnerability for drug experimentation, has not been fully evaluated. Here, we assess the effects of chronic forced exercise during adolescence on preference for cocaine using the conditioned place preference (CPP) paradigm in male and female Lewis rats. The group of rats exposed to exercise ran on a treadmill for 6 weeks on a progressive time-increased schedule for up to 1 h of exercise per day, while the groups of sedentary rats remained in their home cage. Following the 6 weeks of exercise exposure, rats were tested for cocaine CPP. Results showed that chronic exercise significantly attenuated cocaine CPP in both males and females compared to a sedentary environment. Furthermore, male exercise rats failed to show significant cocaine CPP. In contrast, female exercise rats still showed cocaine CPP but it was significantly reduced compared to the female sedentary rats. Females also exhibited greater cocaine CPP than males overall. These findings suggest that strategies to promote physical activity during adolescence may be protective against cocaine abuse in both males and females, and these findings merit further investigation. We also corroborate a gender-specific sensitivity to the reinforcing effects of cocaine, highlighting the need to consider gender-tailored exercise interventions for drug abuse prevention.



## 1. Introduction

It has been well-established that exercise affects dopaminergic activity [1,2]. Since brain dopamine (DA) activity is disturbed in individuals with substance use disorders [3–8] and in animal models of chronic drug exposure, there has been interest in the potential beneficial effects of physical activity in prevention and treatment (adjunct) of substance use disorders (SUD) including a reversal of the neurotoxic effects of drugs [9–12]. Very few studies, however, have tested the effect of exercise on the prevention of SUD and/or as an adjunct in the treatment of SUD. In habitual smokers, acute exercise was reported to decrease nicotine cravings and withdrawal symptoms during and immediately following exercise for up to 30 min [13]. Rodent studies have reported conflicting results. Chronic forced exercise (90 min of treadmill running per day for either 11 or 30 days), beginning at about 2 months of age, resulted in attenuated self-administration of morphine in male Wistar rats [14], and chronic voluntary exercise (6 weeks of access to running wheel in the home cage), beginning at 3 weeks of age, resulted in decreased cocaine self-administration in female Long–Evans rats [15]. Others have found that access to a running wheel during cocaine self-administration has sex-dependent effects; although wheel access decreased cocaine intake in both sexes of Sprague–Dawley rats, it was only significant in females [16]. Voluntary wheel running has also been shown to facilitate extinction and attenuate reinstatement of cocaine self-administration in adult female Wistar rats [17], as well as decrease ethanol preference and consumption in adult male and female C57/BL6 mice during a two-bottle choice paradigm [18]. Conversely, another study reported that chronic voluntary exercise (6 weeks of access to running wheel in the home cage), beginning at 3 weeks of age, increased cocaine conditioned place preference (CPP) in female Long–Evans rats [19]. Similarly, chronic voluntary exercise (3 weeks of access to a running wheel) increases morphine

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CPP in adult male Sprague–Dawley rats [20]. In another study on adult male Lewis rats, voluntary wheel running during a 1 or 2 week ethanol withdrawal period increased subsequent intake of and preference for ethanol in a two-bottle choice paradigm [21]. The factors that explain these different outcomes are not yet clear.

In the present study, we tested the effect of chronic forced treadmill running exercise during adolescence on cocaine CPP in male and female Lewis rats. Forced, rather than voluntary, exercise was chosen so that each rat's exercise speed, frequency, duration, and intensity would be the same. Also, previous studies suggest that forced exercise more closely models the average human exercise regimen, while a voluntary exercise paradigm models highly motivated endurance athletes [22]. We chose to use Lewis rats, as this strain is both addiction-prone and has a high propensity for running [23–26]. We chose the adolescent period since this is the stage in life of greater vulnerability for drug experimentation and thus preventions strategies that could decreases conditioning to initial drug exposures may decrease risks of further use. We also assessed gender differences since women are more susceptible than men to psychostimulant drugs, at all phases of the addiction process, including initiation, maintenance, and relapse [27]. Preclinical studies have also reported sex differences in the acquisition, maintenance, and reinstatement of cocaine self-administration [28–31]. Our hypothesis was that chronic exercise during adolescence would attenuate cocaine CPP, and that this effect may differ between genders.

## 2. Materials and methods

### 2.1. Animals

Male ($n = 24$) and female ($n = 24$) Lewis rats, at 6 weeks of age, were divided into exercise and control sedentary groups. The estrous cycle was not monitored and randomly varied so that findings could be generalized for all phases of the cycle, similar to a recent related study on the effects of voluntary exercise on cocaine self-administration and reinstatement [17]. Food and water were provided ad libitum, and food intake and body weight were monitored daily at 10:00 h. Subjects were individually housed at a temperature of 22.0 °C ± 2 °C and on a 12 h reverse light/dark cycle (lights off: 08:00–20:00 h). The experiment was conducted in accordance with the National Academy of Sciences Guide for the Care and Use of Laboratory Animals (1996) and Brookhaven National Laboratory Institutional Animal Care and Use Committee.

### 2.2. Drugs

Cocaine (Sigma–Aldrich, St. Louis, MO, USA) was dissolved in 0.9% saline for a dosage of 25 mg/kg i.p.

### 2.3. Procedures

#### 2.3.1. Chronic daily treadmill exercise regimen

A custom-made motorized treadmill was used to conduct forced exercise on the experimental rats. The treadmill was divided into six Plexiglas running lanes and running was forced by a piece of sheet metal that acted as a barrier to keep the rats enclosed on the treadmill, as no other stimulus was used to drive running. The treadmill was located in a separate room from housing and later CPP testing. All exercise subjects ($n = 24$; 12 male and 12 female) were conditioned under the same exercise paradigm. Exercise was conducted between 10:00 h and 13:00 h. The treadmill running regimen began at 10 min/day at a steady rate of 10 m/min on a motor-driven treadmill with no incline. This speed is within the range used in previous rat studies [14,32]. The rate was held constant, and the duration of exercise was lengthened by 10 min/day until 60 min/day was reached. Rats were given a ten-minute break after the first half hour of exercise. The exercise-treated rats were maintained on this daily exercise regimen, 5 days per week, for 6 weeks prior to CPP testing. The total distance traveled over the course of the 6-week exercise period was approximately 16,500 m. Sedentary rats remained in their home cages while exercise rats underwent training.

#### 2.3.2. Conditioned place preference (CPP)

The CPP apparatus (Coulbourn Instruments, Allentown, PA, USA) consisted of two compartments (30.5 cm × 26.5 cm × 37 cm) that were connected by a central corridor (12.75 cm × 23 cm × 15.25 cm). The left lateral compartment had black walls and a perforated stainless steel floor with round holes on staggered centers. The central corridor was transparent with a smooth Plexiglas floor, and the right compartment had white walls with a 1 cm-square stainless steel grated floor.

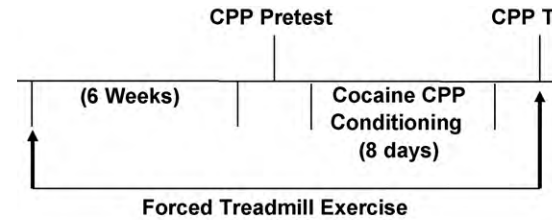


**Fig. 1.** Forced exercise and conditioned place preference timeline. Chronic forced exercise (treadmill running) began 6 weeks prior to a classic conditioned place preference test for cocaine. Exercise was continued throughout the CPP paradigm, as well as after the final CPP test, until all rats were sacrificed.

Guillotine-style doors were used to control access between boxes and the central corridor. Infrared activity monitors measured locomotor activity in each compartment. Experimental variables and data were recorded using Graphic State v2.0 software.

#### 2.3.3. Pretest phase (Day 1)

CPP procedures were as previously described [33] and outlined in Fig. 1. Briefly, at the end of the 6-week exercise regimen, rats were tested for cocaine CPP. The exercise regimen persisted throughout the CPP experiment, ending on the last day of CPP. CPP testing and conditioning occurred at least 90 min after the completion of exercise on any given day to ensure the rats were not fatigued. On the pretest day, rats were removed from their home cages and placed in the central corridor of the CPP apparatus. Free access to the entire apparatus lasted 15 min, after which animals were returned to home cages. Time spent in the black, white, and center compartments was recorded. From the results of the pretest, the box preference for each rat was determined before cocaine conditioning. The chamber in which the rat spent the greatest amount of time during the pretest was defined as the *initially preferred chamber*; conversely, the chamber in which the rat spent less time was defined as the *initially non-preferred chamber*.

#### 2.3.4. Conditioning phase (8 days)

Conditioning lasted a total of 8 consecutive days. Conditioning assignments were based on the results of the pretest, such that each animal was conditioned to associate cocaine with the chamber of the CPP apparatus that was initially non-preferred. On conditioning days, rats either received cocaine (25 mg/kg i.p.), after which they were immediately confined to the initially non-preferred chamber of the CPP apparatus (referred to as the *cocaine-paired chamber*), or saline (i.p.) and placed in the initially preferred chamber of the CPP apparatus (referred to as the *control chamber*). Confinement in the CPP apparatus lasted for 30 min, and the rats were subsequently returned to their home cage. Conditioning occurred on an alternating schedule, such that cocaine administration prior to box confinement was followed by the alternative box confinement the following day, with saline administration. Throughout the CPP conditioning phase, locomotor activity was also measured in each chamber.

#### 2.3.5. Test phase

On the day immediately following the 8 days of conditioning, all rats were tested for CPP. Briefly, rats were placed in the central corridor of the CPP apparatus and allowed free access to all three compartments for 15 min while recording time spent in each. CPP for cocaine was determined by comparing time spent in the cocaine-paired chamber before (pretest phase) and after (test phase) conditioning.

### 2.4. Statistical analysis

Three-way repeated-measures ANOVAs were used to analyze food intake and body weight (between-subjects factors: gender and exercise; within-subjects factor: time). A two-way ANOVA (between-subjects factors: gender and exercise) was used to analyze change in body weight from the beginning to the end of the exercise regimen.

To determine whether each group formed a significant CPP to the cocaine-paired chamber, the CPP data was analyzed using paired $t$-tests to compare the time spent in the paired chamber during the pretest versus test for each group: [(a) exercise females, (b) exercise males, (c) sedentary females and (d) sedentary males]. In addition, differences in the degree of preference formed were assessed by comparing the changes in time spent in the cocaine-paired box from the pretest to the test between the four groups using a two-way ANOVA (factors: sex and exercise).

Finally, a four-way ANOVA (between-subjects factors: gender, exercise, and drug treatment; within-subjects factor: time) was used to analyze locomotor activity during CPP.

When appropriate, ANOVAs were followed by multiple pair-wise comparisons (Holm-Sidak method). Statistical significance was set at $p < 0.05$ and $p$-values are reported when $t$-values were found to be significant.

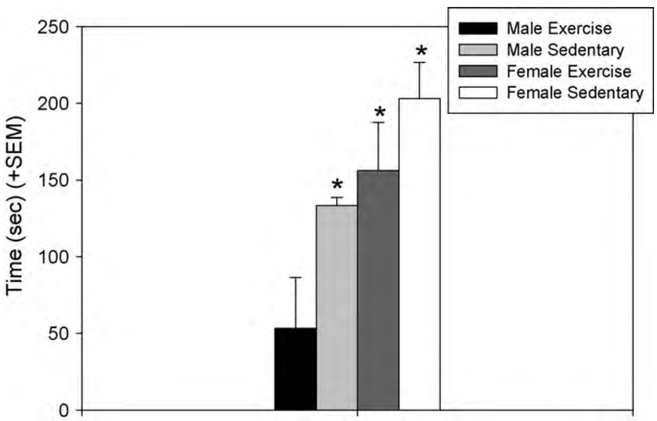


**Fig. 2.** Mean change in time spent in cocaine-paired box before and after conditioning. Sedentary males, sedentary females, and exercise females showed a significant CPP for cocaine (*$p < 0.001$); however, exercise males did not. Exercise attenuated cocaine preference in both sexes ($p = 0.05$), and females exhibited a greater cocaine CPP than males ($p = 0.001$).

## 3. Results

### 3.1. Conditioned place preference

All four groups of animals exhibited an increase in time spent in the paired cocaine-chamber from the pretest to the test (Fig. 2). Paired *t*-tests showed that this increase was significant for sedentary males, sedentary females, and exercise females ($p < 0.001$ for all), but not exercise males. A two-way ANOVA (factors: gender and exercise) was then performed to evaluate differences in the degree of preference for cocaine developed by each group, which revealed a significant main effect of gender [$F(1,42) = 12.336$; $p = 0.001$] and exercise [$F(1,42) = 3.976$; $p = 0.05$], whereas the interaction between gender and exercise was not significant. Pairwise comparisons revealed that exercise decreased cocaine CPP ($p = 0.05$), and that females exhibited greater cocaine CPP than males ($p = 0.001$).

### 3.2. CPP locomotor activity

A four-way repeated measures ANOVA (between-subjects factors: gender, exercise, and drug treatment; within-subjects factor: time) was used to compare locomotor activity exhibited by rats in all four study groups while in their respective CPP chambers following administration of saline (Fig. 3A) or cocaine (Fig. 3B). This ANOVA revealed significant main effects of drug treatment [$F(1,228) = 60.0409$; $p < 0.001$] and gender [$F(1,228) = 8.8236$; $p < 0.01$]; the interactions between time and gender [$F(3,228) = 3.0065$; $p < 0.05$], time and exercise [$F(3,228) = 3.4544$; $p < 0.05$], and time, exercise, and drug treatment [$F(3,228) = 2.8873$; $p < 0.05$] were also significant.

Pair-wise comparisons showed as expected that animals were more active when they received cocaine compared to saline ($p < 0.001$), and males were more active than females ($p < 0.01$; Table 1). Also, exercise had no effect on CPP locomotor activity in response to either saline or cocaine administration on any particular day (Table 1).

### 3.3. Body weight

A three-way repeated measures ANOVA (between-subjects factors: gender and exercise; within-subjects factor: time) revealed there were significant main effects of gender [$F(1,264) = 579.54$; $p < 0.001$] and time [$F(6,264) = 3434.95$; $p < 0.001$], as well as significant interactions between gender and time [$F(6,264) = 787.31$; $p < 0.001$] and gender, exercise, and time [$F(6,264) = 2.54$; $p < 0.05$], on body weight (Fig. 4). Pair-wise comparisons revealed that the mean body weight of each group increased over the course of the study ($p < 0.05$ for all). Males weighed more than females, across all weeks and regardless of exercise treatment ($p < 0.05$ for all). Exercise had no significant effect on the body weight of either males or females, overall or in any specific week. A two-way ANOVA (between-subjects factors: gender and exercise) was used to analyze the percent change in body weight from the beginning to the end of the exercise regimen; the ANOVA revealed a significant effect of gender only [$F(1,42) = 380.934$; $p < 0.001$]. Pair-wise comparisons found that males exhibited a significantly greater per-

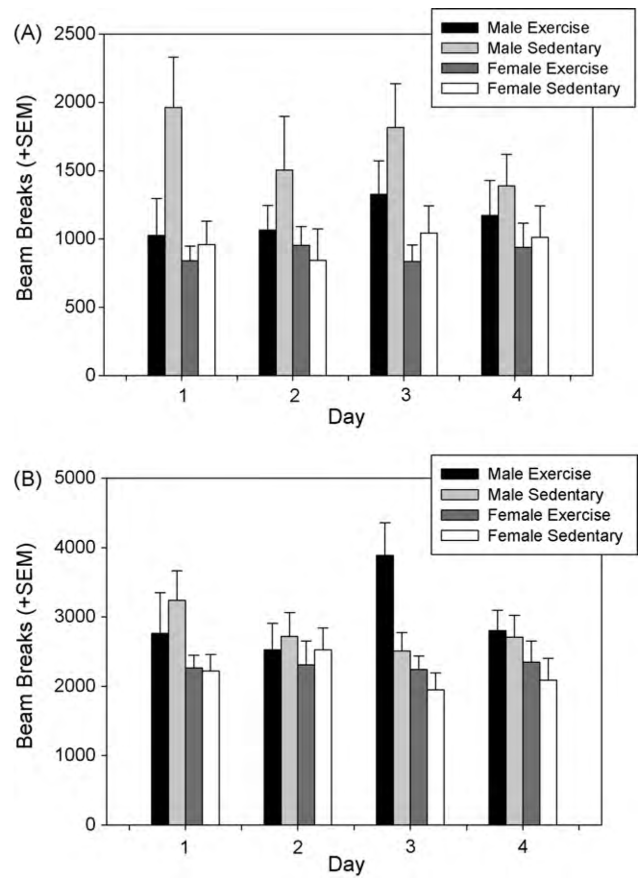


**Fig. 3.** Locomotor activity during cocaine CPP conditioning. Male rats were more active than female rats ($p < 0.001$), and rats were more active on cocaine than saline ($p < 0.001$). (A) Mean locomotor activity over the 4 days on which cocaine was administered. (B) Mean locomotor activity over the 4 days on which saline was administered.

**Table 1**
Locomotor activity during cocaine CPP conditioning.

| | Male exercise | Male sedentary | Female exercise | Female sedentary |
|---|---|---|---|---|
| Saline days | | | | |
| 1 | 1026.9 ± 269.4 | 1961.8 ± 368.3 | 841 ± 106.7 | 958.1 ± 171.6 |
| 2 | 1064.6 ± 180.0 | 1503.9 ± 392.1 | 951.8 ± 139.3 | 841.8 ± 230.8 |
| 3 | 1327.3 ± 243.4 | 1815.3 ± 321.8 | 834.7 ± 122.2 | 1042.9 ± 200.8 |
| 4 | 1171.9 ± 257.1 | 1387.3 ± 230.6 | 938 ± 176.3 | 1010.7 ± 231.4 |
| Cocaine days | | | | |
| 1 | 2760.3 ± 586.6 | 3237.4 ± 425.8 | 2264.9 ± 181.5 | 2216.6 ± 238.1 |
| 2 | 2524.0 ± 380.7 | 2721.2 ± 343.0 | 2308.5 ± 345.1 | 2522.0 ± 320.4 |
| 3 | 3886.3 ± 470.5 | 2506.0 ± 265.5 | 2241.4 ± 192.5 | 1944.3 ± 244.6 |
| 4 | 2802.9 ± 291.5 | 2705.5 ± 317.5 | 2346.6 ± 303.4 | 2087.1 ± 317.1 |

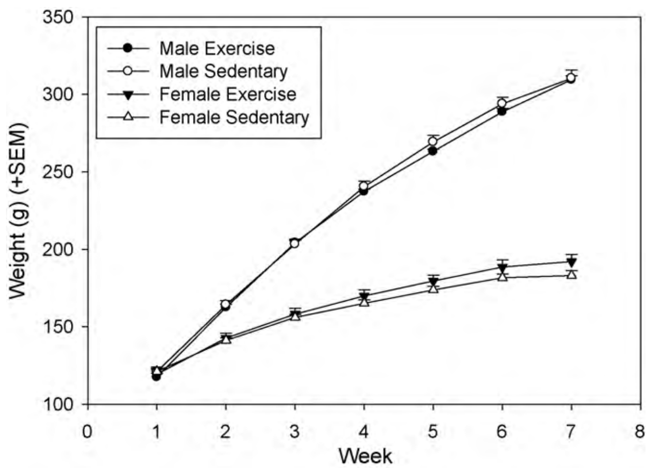


**Fig. 4.** Mean body weight for each of the four groups of rats over the course of the study. All groups gained a significant amount of weight over the study ($p < 0.05$). Male rats weighed significantly more than females ($p < 0.05$).

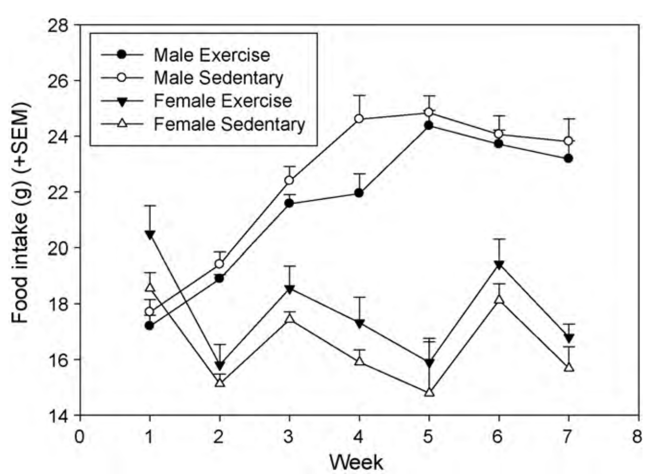


**Fig. 5.** Mean daily food intake for each of the four groups for each week. There was a steady increase in food intake between weeks 1 and 5 exhibited by males ($p < 0.05$); however, female food intake was more erratic weekly. Male rats consumed significantly more food than female rats ($p < 0.05$).

cent change in body weight than females ($p < 0.001$). Mean percent change in body weight (±SEM) for each group was as follows: [exercise males: 144.4 ± 5.7], [sedentary males: 143.4 ± 6.5], [exercise females: 55.6 ± 1.6], [sedentary females: 51.2 ± 1.4].

### 3.4. Food intake

A three-way repeated measures ANOVA (between-subjects factors: gender and exercise; within-subjects factor: time) revealed that there were significant main effects of gender [$F(1,264) = 210.31$; $p < 0.001$] and time [$F(6,264) = 29.855$; $p < 0.001$], as well as significant interactions between gender and exercise [$F(1,264) = 9.78$; $p < 0.01$], and gender and time [$F(16,264) = 58.87$; $p < 0.001$] on food intake (Fig. 5). There was a steady increase in food intake between weeks 1 and 5 exhibited by males ($p < 0.05$); however, female food intake was more erratic weekly. Males consumed more food than females, across all time points and regardless of exercise treatment ($p < 0.05$ for all). There were no significant differences between exercise and sedentary animals, regardless of gender or time.

## 4. Discussion

### 4.1. Cocaine conditioned place preference

Here, we show that chronic forced exercise during adolescence decreases preference for cocaine in male and female Lewis rats, and inhibits the formation of cocaine preference altogether in males but not females. Our findings are in contrast to those of a prior study that reported that chronic *voluntary* exercise increased cocaine CPP (10 mg/kg i.p.) in female adolescent Long–Evans rats that were exposed to exercise for 6 weeks, beginning at 3 weeks of age [19]. These studies differed in exercise type, rat strain, age, and cocaine dose. Our findings were consistent, however, with prior studies showing that chronic exercise decreased self-administration of morphine [14] and cocaine [15], and facilitated extinction and attenuated reinstatement of cocaine self-administration [17]. This general trend supported our hypothesis that exercise may be beneficial in the prevention of substance abuse disorders. This hypothesis was based upon previous reports that physical exercise increased functioning of the DA system, and evidence that low striatal D2 receptor levels were associated with compulsive behaviors such as a wide range of addictions, as well as compulsive eating [3–8,34–37]. Chronic exercise has been shown to increase DA transmission and D2R mRNA, as well as lead to behavioral recovery, in MPTP-lesioned rats [38]. Endurance training resulted in increased striatal D2 binding [39] and attenuated the loss of D2R associated with aging in rats [40]. Similarly, it has also been found that 6 weeks of voluntary exercise increases DA synthesis, reduces D2 autoreceptor-mediated inhibition of DA neurons in the substantia nigra pars compacta, and increased postsynaptic D2 mRNA in the caudate putamen [41]. Future studies are needed to assess if the attenuated cocaine CPP exhibited by animals treated with exercise is associated with changes in dopamine function, including upregulation of D2R in the striatum.

Female rats exhibited significantly greater CPP compared to male rats, and exercise inhibited but did not block cocaine CPP in females. These findings are consistent with reports that women were more vulnerable than men to psychostimulant drugs, at all phases of the addiction process, including initiation, maintenance, and relapse [27]. Similarly, in rats, sex differences in acquisition, maintenance, and reinstatement of cocaine self-administration have been reported [28–31]. Clinical studies have found that cocaine cues induce greater cravings in female compared to male drug addicts [42], which supports our findings since the CPP paradigm pairs the drug with an associated environment.

Another important consideration is that studies on adult Sprague–Dawley and Long–Evans rats have found that females run significantly more than males when given free access to a running wheel [43–46]. Considering female rats' higher propensity for running, it is possible that the level of exercise that was sufficient in the males to inhibit the formation of cocaine CPP was not as strenuous to exert equal effects on the females.

### 4.2. CPP conditioning locomotor activity

There was a significant effect of drug treatment on CPP locomotor activity, with rats that received cocaine exhibiting increased activity over rats that received saline. This was expected, as DA release in the nucleus accumbens is responsible for the locomotor-activating effects of drugs [47–49], as seen in previous cocaine CPP studies [50,51]. We did not observe a sensitization to cocaine in any group, as has been seen in previous studies using similar doses of cocaine in a CPP paradigm in Lewis rats [52]. It is possible that the apparent lack of sensitization may have been likely due to stereotypy behavior, which was not detectable with our apparatus. There is evidence that a high dose of cocaine, such as the one that was used for this study, can cause increased stereotypy that can inhibit other forms of activity [53,54]. Overall, male rats were more active than female rats, which was the opposite of what was observed in Fischer rats who showed greater locomotor activity in females than in males in a cocaine CPP paradigm [55]. One possible explanation for this discrepancy is the fact that there is a significant difference in the cocaine dose given in the aforementioned study (5 mg/kg for females and 20 mg/kg in males) and the one used in our study (25 mg/kg for both genders). It is possible that the hyper-threshold dose of cocaine was less than optimal for producing locomotor hyperactivity in female rats. Another difference in the two studies that could result in this discrepancy is the difference in strain. It has been shown that Lewis rats exhibit significantly greater cocaine sensitization (i.e. increased locomotor activity) and are more sensitive to the reinforcing effects of drugs than Fischer rats [56]. Finally, the difference in age may play a role: the rats in our study were 12 weeks old at the time of CPP whereas the ones from Russo et al. were 8 weeks old. It is interesting to note that the male exercise rats did not exhibit significantly different locomotor activity than any other group when administered cocaine, even though they showed significantly less CPP. This indicates that the neurobiological underpinnings of these two processes are distinct.

### *4.3. Body weight*

As expected, male rats weighed more than female rats, and all groups gained weight as they grew from adolescents to adults. Our study found that exercise had no effect on the body weight of either sex. Previous studies have found that chronic forced exercise decreases body weight [57–59]; however, in these studies exercise was more strenuous (2–6 h per day of forced swimming) than what rats were exposed to in our study.

### *4.4. Food intake*

As expected, males consumed larger amounts of food than females. The overall trend in food intake for male rats was a general increase over the 7-week period. For the female rats, the trend in food intake over the 7 weeks of the study was more erratic; however, the difference in food intake from week to week was generally not greater than five grams. This level of variation has been observed in other studies where food intake was measured over a long period of time [60,36]. Exercise had no significant effect on food intake, which was also seen in a previous study on male Sprague–Dawley rats exposed to 2 h/day, every other day, of forced swimming exercise for 4 and 10 weeks [59].

In summary, the present study concludes the following: (1) Chronic forced exercise during adolescence blocks the formation of cocaine CPP in males during young adulthood. (2) Chronic forced exercise in adolescence decreases cocaine CPP, but does not eliminate its formation altogether, in young adult females. (3) There is a gender difference in cocaine CPP, such that female rats exhibit greater preference than males. These findings suggest that strategies to promote physical activity during adolescence may be protective against cocaine abuse and merits further investigation. Our findings also corroborate a gender-specific sensitivity to the reinforcing effects of cocaine, highlighting the need to consider gender-tailored exercise interventions for prevention of drug abuse.

## Acknowledgments

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